This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims

Claim 1 (Currently amended):

A method of making a chimeric mouse, comprising:

a. creating an immunetolerant mouse lacking functional T and B cells and having a genome which comprises a urokinase-type plasminogen activator (uPA) gene, expression of said uPA gene resulting in liver degeneration; and

b. repopulating the parenchyma of the degenerated liver by transplanting xenogenic mammalian hepatocytes that are a natural host for infection with one or more compatible hepatitis virus into said liver; thereby making said chimeric mouse

~~transplanting xenogenic mammalian hepatocytes to repopulate the parenchyma of the degenerated liver, said xenogenic mammalian hepatocytes being infected with at least one compatible mammalian hepatitis virus~~.

Claim 2 (Currently amended): The method of claim 1, ~~which~~ further comprising ~~comprises~~ infecting the xenogenic mammalian hepatocytes with hepatitis virus prior to said transplanting.

Claim 3 (Currently amended): The method of claim 1, ~~which~~ further comprising ~~comprises~~ infecting the xenogenic mammalian hepatocytes with hepatitis virus following said repopulation.

Claim 4 (Currently amended): The method of claim 1, ~~which comprises selecting~~ wherein the xenogenic mammalian hepatocytes are selected from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrel, and woodchuck hepatocytes.

Claim 5 (Original): The method of claim 1, wherein the compatible mammalian hepatitis virus is at least one of a compatible mammalian hepatitis A virus, hepatitis C virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus or hepadnavirus.

Claim 6 (Original):

The method of claim 1, wherein the immunetolerant mouse which has a degenerated liver is created by:

a. crossing a hemizygous or homozygous urokinase-type plasminogen activator (uPA) transgenic mouse with a homozygous Recombination Activation Gene 2 (RAG-2) knockout mouse to generate F1 uPA hemizygous, RAG-2 hemizygous sibling mice; and

b. crossing the F1 mouse to another sibling F1 mouse or to a RAG2 homozygous mouse to generate a uPA hemizygous or homozygous, RAG2 homozygous (uPA/RAG2) F2 mouse.

Claim 7 (Original): The method of claim 6, wherein the xenogenic mammalian hepatocyte is from a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).

Claim 8 (Previously amended): A chimeric mouse model system for hepatitis comprising an immunetolerant mouse lacking functional T and B cells having a degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of said immunetolerant mouse, said degenerated liver being repopulated with transplanted xenogenic mammalian hepatocytes that are infected with a compatible mammalian hepatitis virus.

Claim 9 (Original): The chimeric mouse model system of claim 8, wherein the xenogenic mammalian hepatocytes are infected with hepatitis virus prior to said transplantation.

Claim 10 (Original): The chimeric mouse model system of claim 8, wherein the xenogenic mammalian hepatocytes are infected with hepatitis virus following said repopulation.

Claim 11 (Original): The chimeric mouse model system of claim 8, wherein the xenogenic mammalian hepatocytes is a member selected from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrel, and woodchuck hepatocytes.

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Claim 12 (Original): The chimeric mouse model system of claim 8, wherein the compatible mammalian hepatitis virus is at least one of a compatible mammalian hepatitis A virus, hepatitis C virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus or hepadnavirus.

Claim 13 (Currently amended): The chimeric mouse model system of claim 8, wherein the immunetolerant mouse having degenerated liver parenchyma is hemizygous or homozygous for said urokinase-type plasminogen activator (uPA) gene and is homozygous for ~~the~~ a Recombination Activation Gene 2 (RAG-2) knockout ~~gene~~ mutation.

Claim 14 (Original): The chimeric mouse model system of claim 13, wherein the source of the xenogenic mammalian hepatocytes is a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).

Claim 15 (Currently amended):

A method for screening a test compound for anti-viral activity, comprising:

a. administering said test compound to an immunetolerant chimeric mouse lacking functional T and B cells which has a degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of said

immunetolerant chimeric mouse, said degenerated liver being repopulated with transplanted xenogenic mammalian hepatocytes that are infected with at least one compatible mammalian hepatitis virus; and

b. assaying the level of replication of the virus; thereby screening said test compound for anti-viral activity.

Claim 16 (Original): The method of claim 15, wherein the mammalian virus is at least one hepatitis virus.

Claim 17 (Original): The method of claim 15, which comprises comparing the level of viral replication in said mouse and in a control mouse which has not been administered the test compound.

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Claim 18 (Original): The method of claim 15, which comprises infecting the xenogenic mammalian hepatocytes with the compatible mammalian virus prior to said transplanting.

Claim 19 (Original): The method of claim 16, which comprises infecting the xenogenic mammalian hepatocytes with the compatible mammalian virus following said repopulating step.

Claims 20 (Original): The method of claim 15, which comprises selecting the xenogenic mammalian hepatocyte from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrel, and woodchuck hepatocytes.

Claim 21 (Original): The method of claim 15, wherein the compatible mammalian virus is at least one of a compatible mammalian hepatitis A virus, hepatitis C virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus or hepadnavirus.

Claim 22 (Currently amended): The method of claim 15, wherein the immunetolerant mouse which has a degenerated liver is hemizygous or homozygous for said urokinase-type plasminogen activator (uPA) gene and homozygous for ~~the~~ a Recombination Activation Gene 2 (RAG-2) knockout ~~gene~~ mutation.

Claim 23 (Original): The method of claim 22, wherein the source of the xenogenic mammalian hepatocytes is a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).

Claim 24 (Original): The method of claim 15, wherein the antiviral compound is a member selected from the group consisting of interferons, cytokines, interleukins, growth factors, hormones, nucleoside analogues, and antisense DNA/RNA.

Claim 25 (Currently amended):

A method for screening a test compound for anti-cancer activity, comprising:

a. administering said test compound to immunetolerant chimeric mice lacking functional T and B cells which have degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of said immunetolerant chimeric mice that is repopulated with transplanted xenogenic mammalian hepatocytes that are infected with at least one compatible mammalian hepatitis virus capable of causing hepatocellular carcinoma in said xenogenic hepatocytes; and

b. assaying said mice for the development of hepatocellular carcinoma virus; thereby screening said test compound for anti-cancer activity.

Claim 26 (Original): The method of claim 25, which comprises comparing the presence of unique viral DNA integrations in the liver of said mouse and in a control mouse which has not been administered the test compound.

Claim 27 (Original): The method of claim 25, wherein the chimeric mouse has precancerous or malignant cancerous hepatic tissue and wherein the development of hepatocellular carcinomas is assayed by monitoring for the prevention of the development of cancerous tissue from precancerous tissue or the amelioration of the malignant cancerous tissue.

Claim 28 (Original): The method of claim 27, which comprises comparing the assay in the chimeric mouse with the same assay carried out in a control mouse which has not been administered the test compound.

Claim 29 (Original): The method of claim 25, which comprises infecting the xenogenic mammalian hepatocytes with a hepatitis virus prior to said transplantation step.

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Claim 30 (Original): The method of claim 25, which comprises infecting the xenogenic mammalian hepatocytes with hepatitis virus prior to said transplanting step.

Claim 31 (Original): The method of claim 25, which comprises infecting the xenogenic mammalian hepatocytes are infected with hepatitis virus following said repopulating step.

Claim 32 (Original): The method of claim 25, which comprises selecting the xenogenic mammalian hepatocyte from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrels and woodchuck hepatocytes.

Claim 33 (Original): The method of claim 25, wherein the compatible mammalian hepatitis virus is at least one of a compatible mammalian hepatitis A virus, hepatitis C virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus or hepadnavirus.

Claim 34 (Currently amended): The method of claim 25, wherein the immunetolerant mouse which has a degenerated liver is hemizygous or homozygous for said

urokinase-type plasminogen activator (uPA) gene and homozygous for ~~the~~ a Recombination Activation Gene 2 (RAG-2) knockout ~~gene~~ mutation.

Claim 35 (Original): The method of claim 33, wherein the source of the xenogenic mammalian hepatocytes is a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).

Claim 36 (Original): The method of claim 25, wherein the anticancer compound is a member selected from the group consisting of interferons, cytokines, interleukins, growth factors, hormones, nucleoside analogues, and antisense DNA/RNA.

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Claim 37 (Currently amended):

A method of making a chimeric mouse, comprising:

a. creating an immunetolerant mouse, said immunetolerant mouse lacking functional T and B cells and having a genome which comprises a urokinase-type plasminogen activator (uPA) gene, expression of said uPA gene resulting in liver degeneration; and

b. repopulating the parenchyma of the degenerated liver by transplanting xenogenic mammalian hepatocytes that are a natural host for infection with one or more compatible hepatitis virus into said liver; thereby making said chimeric mouse.

Claim 38 (Currently amended): A chimeric mouse model system for hepatitis comprising an immunetolerant mouse lacking functional T and B cells,

said immunetolerant mouse having a degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of said immunetolerant mouse, and

said degenerated liver ~~is~~ being repopulated with transplanted xenogenic mammalian hepatocytes that are a natural host for infection with one or more compatible hepatitis virus.

Claim 39 (Currently amended):

A method of making a chimeric mouse, comprising:

a. creating an immunetolerant mouse, said immunetolerant mouse having a degenerated liver due to expression of a urokinase-type plasminogen activator (uPA) gene and lacking functional T and B cells, said uPA gene being present in the genome of said immunetolerant mouse; and

b. transplanting human hepatocytes having at least 80% viability by intrasplenic injection to repopulate the parenchyma of the degenerated liver; thereby making said chimeric mouse.

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Claim 40 (Previously added): The method of claim 39 wherein said immunetolerant mouse is about 10-14 days old at the time of transplanting said human hepatocytes.

Claim 41 (Previously added): The method of claim 40 wherein the transplanted human hepatocytes reconstitute approximately 10% of the degenerated liver.

Claim 42 (Previously added): The method of claim 1 wherein said uPA gene encodes secreted uPA.

Claim 43 (Previously added): The chimeric mouse model system of claim 8 wherein said uPA gene encodes secreted uPA.

Claim 44 (Previously added): The method of claim 15 wherein said uPA gene encodes secreted uPA.

Claim 45 (Previously added): The method of claim 25 wherein said uPA gene encodes secreted uPA.

Claim 46 (Previously added): The method of claim 37 wherein said uPA gene encodes secreted uPA.

Claim 47 (Previously added): The chimeric mouse model system of claim 38 wherein said uPA gene encodes secreted uPA.

Claim 48 (Previously added): The method of claim 39 wherein said uPA gene encodes secreted uPA.